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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Valerie CHEYNET-SAUVION et al.

Group Art Unit: 1655

Application No.: 09/402,131

Examiner: B. Sisson

Filed: December 8, 1999

Docket No.: 104458

For: RNA-DEPENDENT RNA POLYMERASE FUNCTIONING PREFERABLY ON
RNA MATRIX AND PROMOTER-DEPENDENT TRANSCRIPTION PROCESS
WITH SAID RNA-DEPENDENT RNA POLYMERASE

SUBMISSION OF ORIGINAL DECLARATION

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

Submitted herewith is the original signed Declaration Under 37 C.F.R. §1.132 for the
above-identified application. This Declaration corresponds to the facsimile copy of the
Declaration filed on January 23, 2003.

Respectfully submitted,

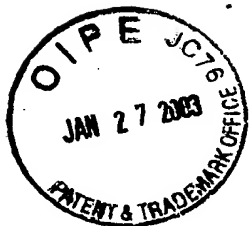
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Date: January 27, 2003

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SAID RNA-DEPENDENT RNA POLYMERASE

DECLARATION UNDER 37 C.F.R. §1.132

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

I, William T. McAllister, a citizen of the United States of America, hereby declare and
state:

1. My qualifications are set forth in the attached curriculum vitae.
2. I am an inventor of the above-identified patent application.
3. I am familiar with its contents and the contents of the pending Office Action
and the accompanying Amendment After Final Rejection under 37 C.F.R. 1.116.
4. I have read and understand the attached references, and believe that the
teachings of the attached references represent the state of the art at the time the application
was filed. I believe that the specification as originally filed fully enabled one skilled in the art
to make and use the invention as recited in the claims as amended by the accompanying
Amendment After Final Rejection for the reasons set forth below.
5. One skilled in the art would have understood that RNA polymerases encoded
by bacteriophage T7 and its relatives have many common structural and functional features.

The promoter sequences recognized by these phage polymerases, such as T7, T3, K11, SP6 and BA14 phage polymerases, all share a common 23 bp consensus sequence between nucleotides -17 to +6 (see e.g., McAllister, *Cellular and Molecular Biology Research* (1993) 39: 385-391). Because of the structural and functional similarities of the RNA polymerase encoded by these bacteriophages those skilled in the art refer to these RNA polymerases as "T7-like RNA polymerases" and to the phages as "T7-like bacteriophages." (See e.g., Chamberlin et al. (copy submitted with June 5, 2001, Amendment) at page 88, first paragraph, and page 89, Heading 11). Thus, referring to the RNA polymerase as "T7-like phage polymerase" would clearly have been understood by one skilled in the art as referring to the RNA polymerases encoded by T7 and its related phages.

6. In addition to recognizing this consensus sequence within the transcription promoter sequence, T7-like phage RNA polymerases also have a common organization. It is known in the art that these RNA polymerases consist of a single subunit (see e.g., Severinov, PNAS, (2000) 98: 5-7; Tahirov et al., Nature (2002) 420:43-50; and Yin et al., Science (2002) 298: 1387-1395). These references show that there are two "families" of DNA-dependent RNA polymerases that are recognized in the art. One family of polymerases encompasses the T7-like phage polymerases, which consist of a single subunit, while the second family of RNA polymerases covers bacterial and eukaryotic RNA polymerases, which consist of multiple subunits. As described in the specification at, for example, page 4, line 30 to page 53, the T7-like phage polymerases are an art-recognized class of very homologous enzymes. This is also supported by the discussion in Chamberlin et al., from page 89 to 91. Furthermore, Severinov, Tahirov et al. and Yin et al. further demonstrate and confirm the accuracy of this grouping of phage RNA polymerases. Thus, those skilled in the art would have recognized that the T7-like phage polymerases are a closely related group of RNA polymerases.

7. The ability to synthesize a polymer of nucleotides is conferred by the active site of the enzyme, which is highly conserved among the T7-like phage polymerases. An alignment of the RNA polymerases from exemplary T7, T3, SP6 and K11 RNA polymerases is attached. The alignment shows that the amino acid sequence from residue 620 to about 640 is highly conserved across the different types of T7-like phage polymerases.

8. The conserved amino acid sequence in this region of the T7-like phage RNA polymerases would also have suggested to one skilled in the art that similar changes made in the phage polymerases would result in the same or similar mutant phenotypes. Thus, one skilled in the art would have reasonably expected that a mutation at R627 in the manner described in the specification with respect to T7 RNA polymerase would result in a similar mutant phenotype as that of the T7 RNA polymerase in other T7-like phage polymerases. It is a generally accepted and routine practice among those skilled in the art to compare the amino acid sequence of related proteins to localize areas of importance and interest.

9. The skilled artisan would have determined an appropriate mutagenesis strategy based on the comparison of the amino acid sequences and structures. Thus, there would have been no need for the skilled artisan to examine multiple mutations at every possible position within the protein as asserted in the Office Action. The demonstration of one mutant of T7 RNA polymerase activity within a highly conserved region of the amino acid sequence shared by the T7-like phage RNA polymerases would have been expected to yield similar results in other T7-like phage polymerases. Thus, no undue experimentation would have been necessary to practice the claimed invention with various alternative T7-like phage polymerases.

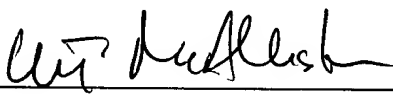
10. The specification describes the modification of a T7 RNA polymerase at residue R627. As a result of this modification, the RNA dependent RNA polymerase activity of T7 RNA polymerase is greatly enhanced. As discussed above, this particular residue lies

within the highly conserved region, between amino acid residues 620 to about 640, that is shared by the T7-like phage RNA polymerases. Thus, one skilled in the art would have expected that the same or similar modification in the highly conserved regions within a different, but related, T7-like phage RNA polymerase would also enhance the RNA dependent RNA polymerase activity in the related T7-like phage RNA polymerase.

11. Thus, in view of the attached references, the specification as filed provides a fully enabling disclosure for the claimed invention. One skilled in the art would not have required further guidance or examples, nor would undue experimentation have been required to practice the claimed invention beyond what is disclosed in the specification.

12. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 1/21/03



William T. McAllister